



# PDBP at UT Southwestern

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# Overall Design

- Two part project
  - Clinical phase: recruit subjects with PD for clinical characterization and biospecimen collection
  - Basic discovery phase: identification of antibody biomarkers using high-throughput screening of a combinatorial peptoid library

# Clinical Phase

- Three movement disorders fellowship-trained neurologists will recruit subjects



Richard Dewey



Shilpa Chitnis



Pravin Khemani

# Recruitment Goals

- We aim to each recruit about one patient per week for 40 weeks of years 1 and 2
- This should achieve 120 subjects by the end of year 1 with 240 subjects enrolled by the end of year 2
- We plan to invite largely local residents with no plans to move away from the Dallas-Ft. Worth area
- We intend to follow subjects for 3-5 years until completion of the project, or longer if we can extend it
- Once a subject is enrolled, we will employ strategies learned from NET-PD LS1 to enhance retention

# Inclusion Criteria

- A diagnosis of idiopathic PD meeting UK PD Society Brain Bank Criteria (Step 1, Step 2, and 2 items present from step 3)
- Male or female age 30 years or older at time of PD diagnosis, (H&Y) stage I-IV
- Clinical evidence of response to dopaminergic medication (MAO-B inhibitors, dopamine agonists, levodopa, or combinations) in patients on treatment for PD
- Confirmation from I-123 Ioflupane SPECT (DatScan®) of dopamine transporter deficit for de-novo, untreated patients
- Able to make visits to UT Southwestern every 6 months for up to 5 years without undue hardship

# Exclusion Criteria

- Idiopathic PD, H&Y stage 5, as these will be unable to participate in gait assessments
- Confirmed or suspected atypical parkinsonian syndromes due to drugs, metabolic disorders, encephalitis, or degenerative diseases
- Presence of definite dementia (MoCA < 17)

# Special Populations Targeted

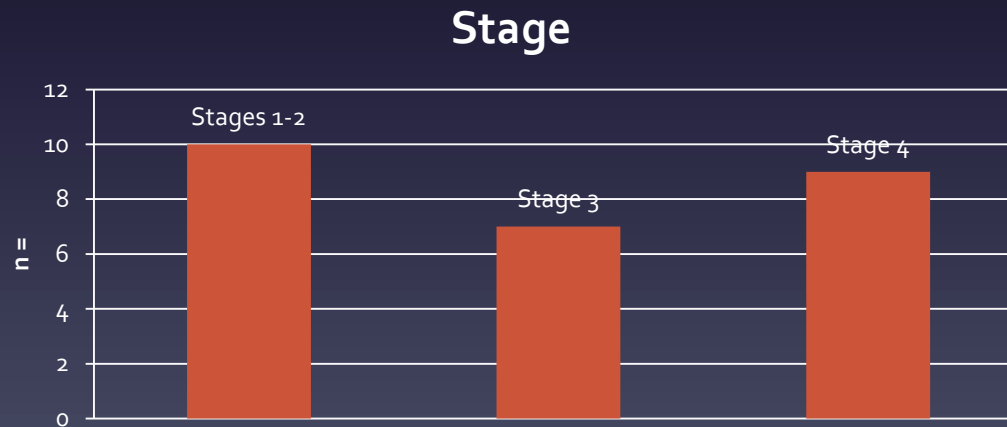
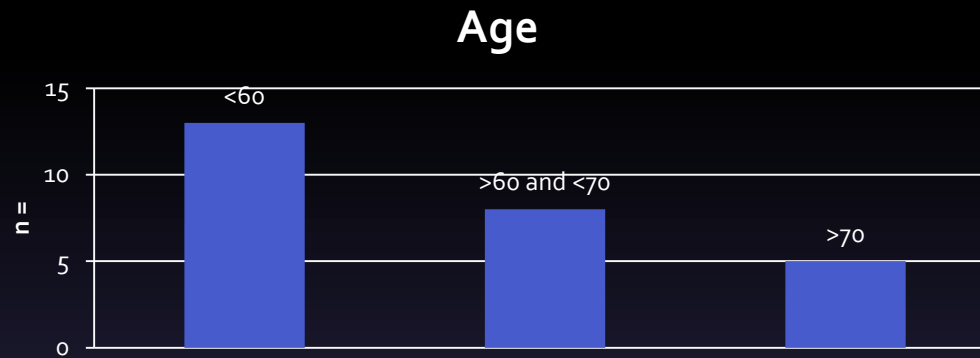
- Datscan<sup>®</sup>-proven idiopathic PD, de-novo, untreated patients (recruitment goal: 20)
- Subjects with and without dyskinesias
- Younger and older subjects
- Early and later stage subjects
- Subjects with hallucinations
- Minority subjects

# Balancing Special Populations

- Investigators and study staff will have a monthly meeting to track recruitment progress and numbers of subjects in special populations
- Graphs will be shown of subjects grouped by special populations and special efforts will be made in the next month to recruit subjects to balance populations



# Balancing Efforts



# NINDS Common Data Elements

- Demographics
- Medical History
- Family History
- Behavioral History
- Neurological Exam
- Vital signs
- Medication review
- Hoehn and Yahr staging
- MDS-UPDRS
- Hamilton depression rating scale
- Hamilton anxiety rating scale
- Montreal Cognitive Assessment (MoCA)
- Epworth Sleepiness Scale
- REM Sleep Behavior Disorder Questionnaire
- PDQ-39
- Schwab and England ADL scale
- UPSIT

# Biospecimen Collection

- Blood: collected every 6 months
  - Blood plasma/serum
  - Whole blood for DNA extraction
  - Whole blood for other studies
  - Pax-gene tube for RNA
- CSF: collected on 100 subjects at baseline and annually for 3 years

# Special Data Collected

- Videotape of the MDS-UPDRS
- APDM Mobility Lab gait analysis
  - iTUG
  - iSWAY

# APDM Mobility Lab

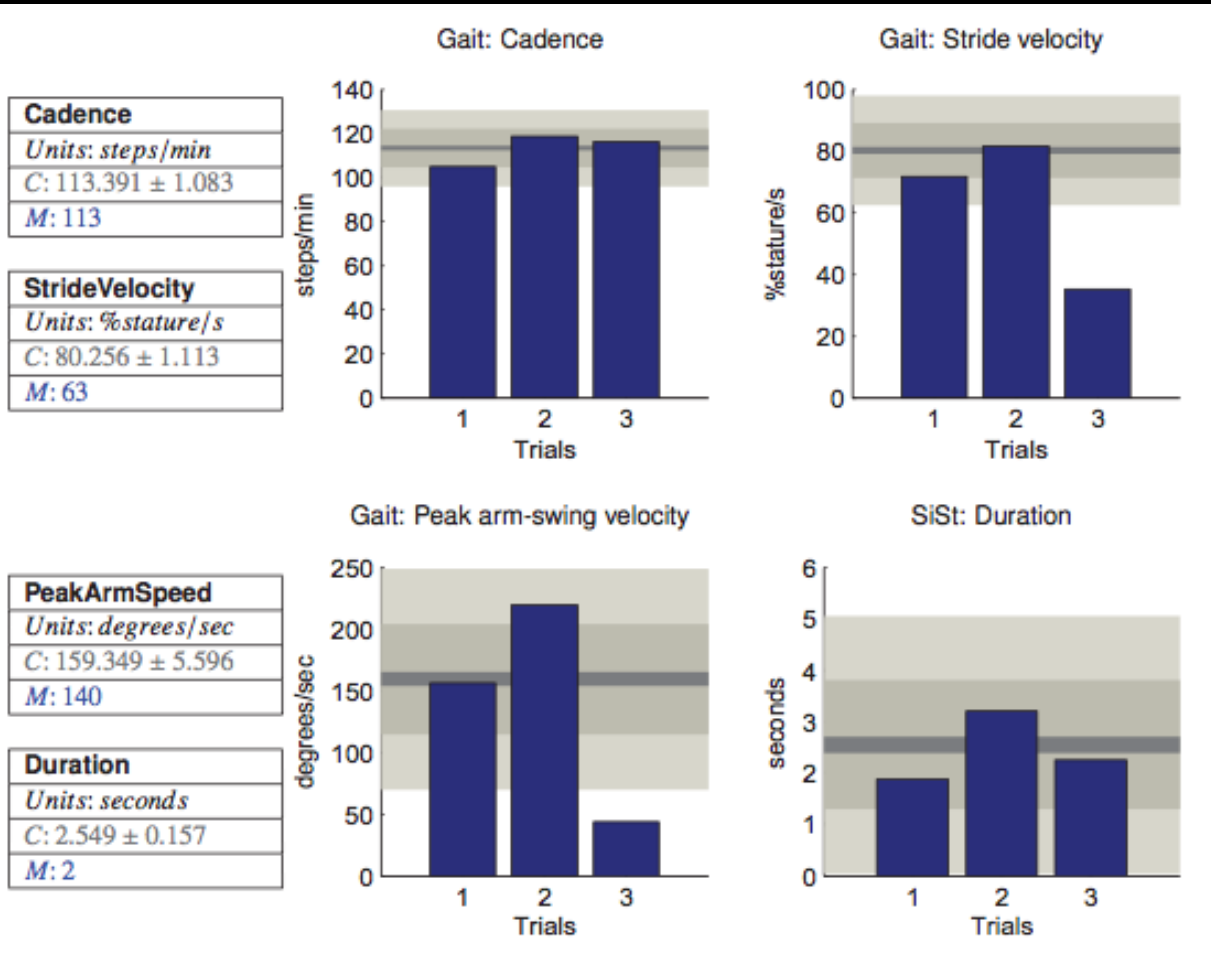
Portable accelerometers attach as shown and movement parameters are recorded wirelessly by a computer



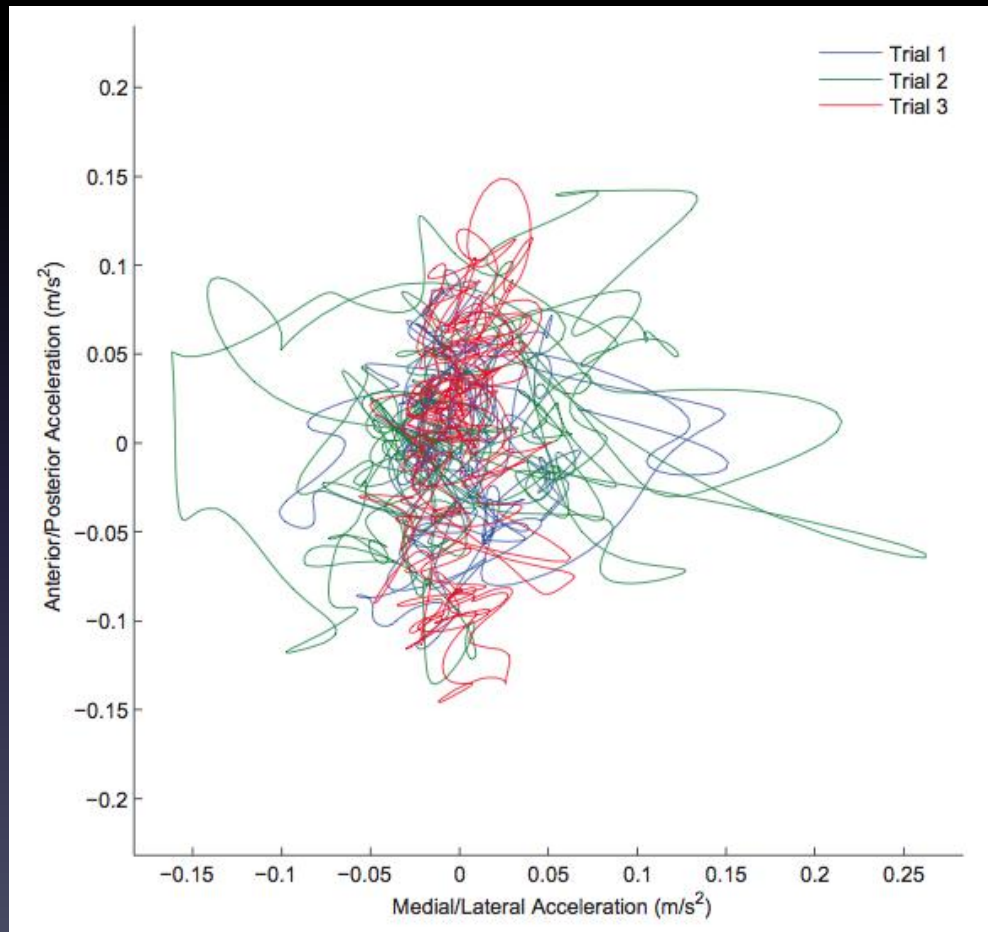
# Mobility Lab Assessments

- iTUG: instrumented timed-up-and-go test provides detailed measurements of
  - Cadence
  - angular velocity of arm-swing
  - turning duration
  - time to perform turn-to-sits
- iSWAY: instrumented analysis of postural sway while standing still

# iTUG Example Output



# iSWAY Example Output





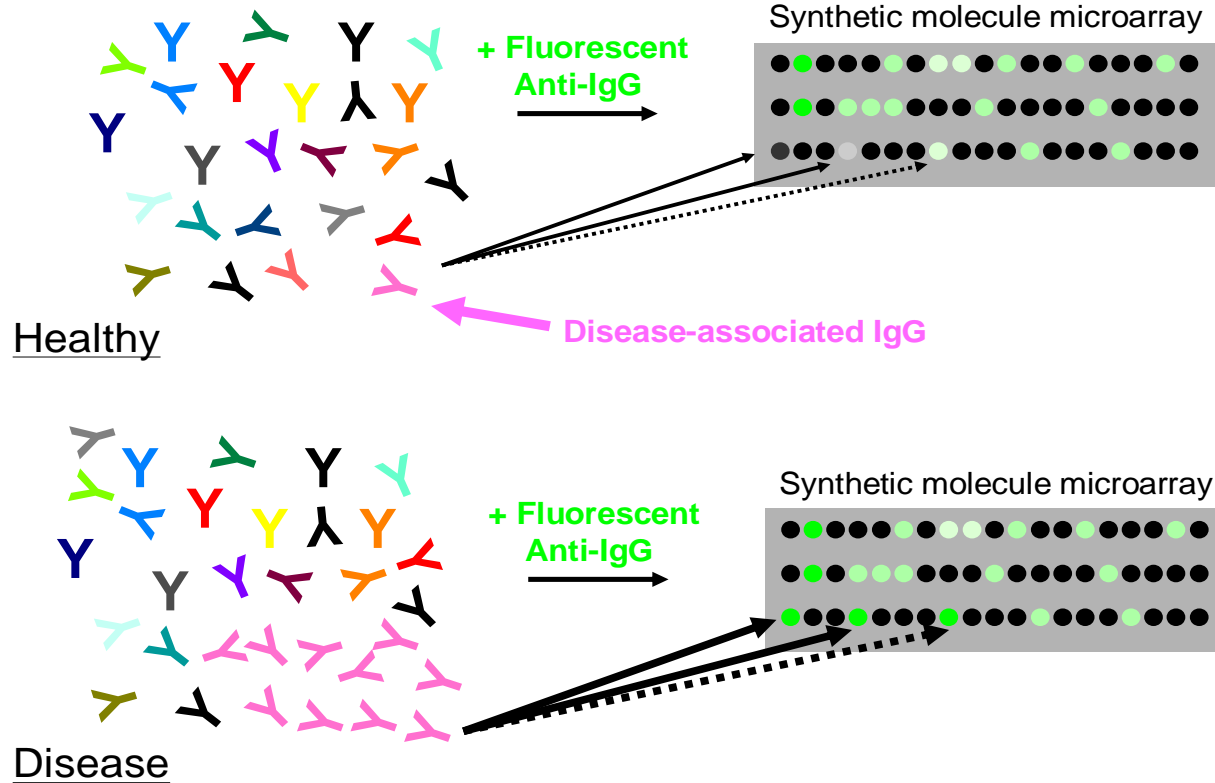
# Clinical Analysis Plan

- Primary objective: To estimate the mean rates of change and the variability around the mean of clinical outcomes in PD patients over 3-5 years of follow-up comparing these rates between PD patients of special populations
  - Early vs late stage
  - Dyskinesias present vs absent
  - Hallucinations present vs absent
  - Younger vs older
  - Minority race vs Caucasian race

# Basic Discovery Phase

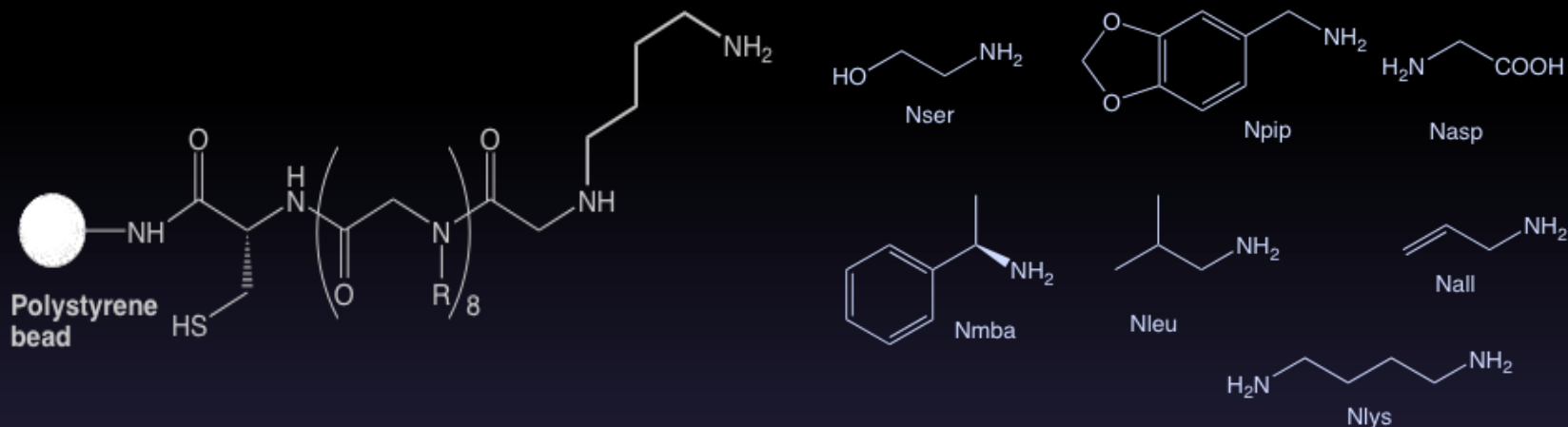
- Antibodies in the blood to PD-related proteins may be useful biomarkers.
- A peptoid library can be used to identify specific antibodies that are elevated in the serum of PD patients.
- Identification of the antibodies that are bound to the peptoids can provide insight into the cause or progression of the disease.

## Peptoid Libraries As Analytical Tools



**Peptoid microarray principle.** Autoantibodies (pink) are anticipated to be amplified in the serum of individuals with a particular disease relative to normal controls. Thus, we look for compounds in a combinatorial library that bind much higher levels of serum IgGs from a “diseased” sample than from a healthy control. Illustrated is an analysis in a microarray format.

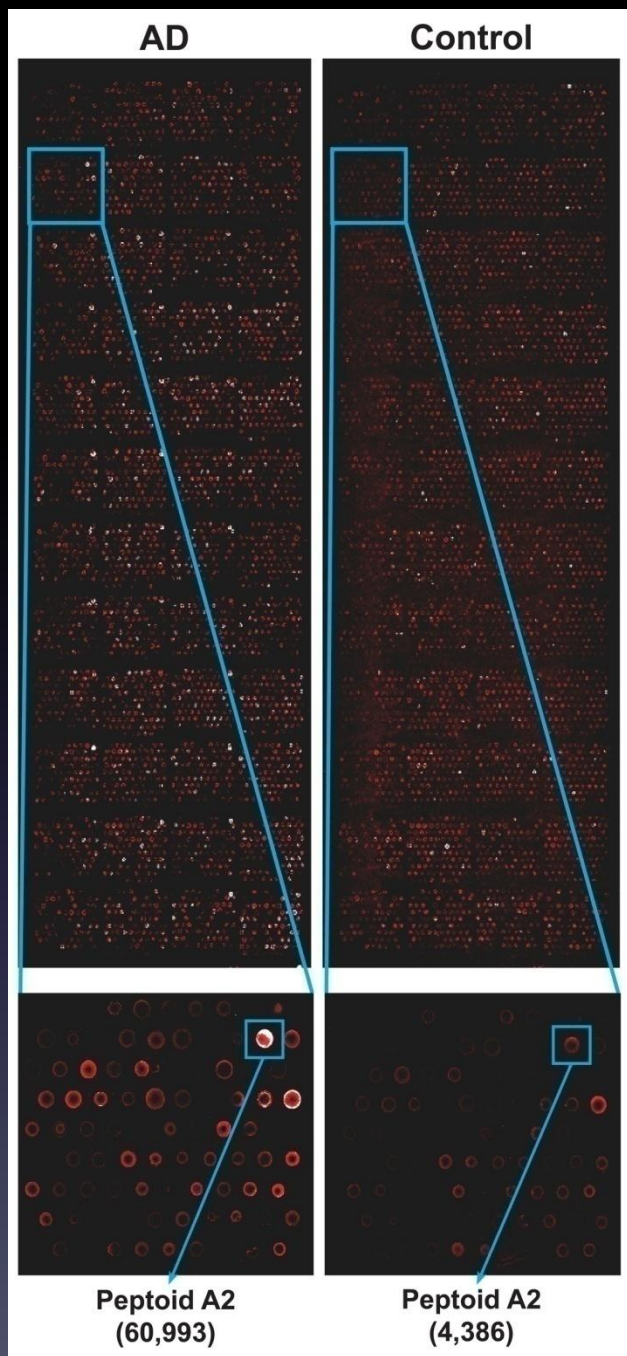
# Peptoid library



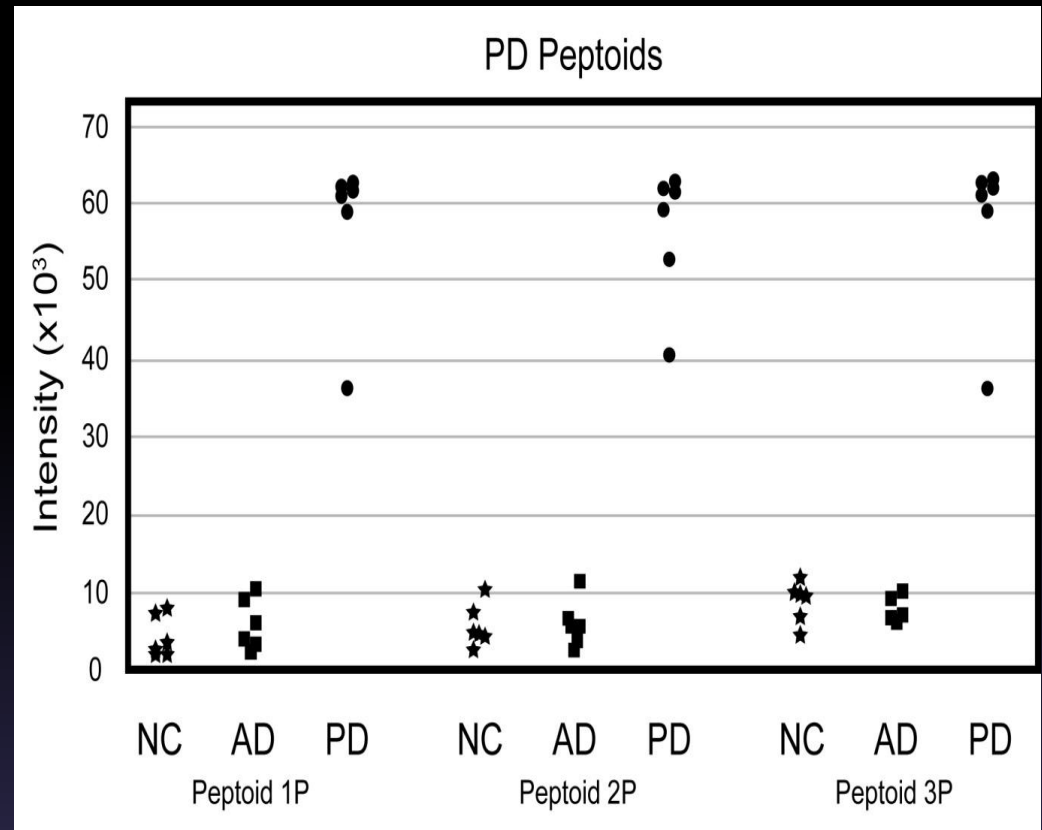
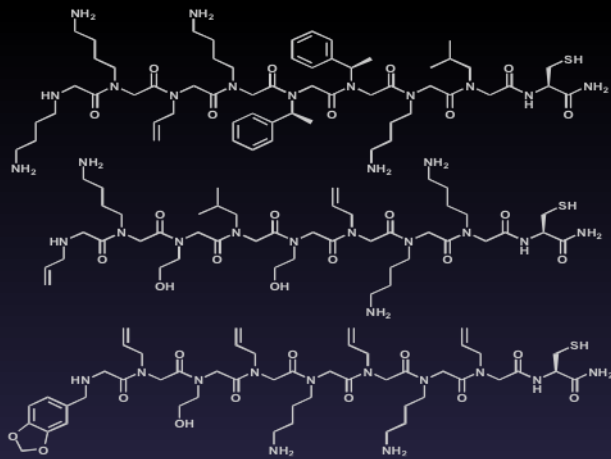
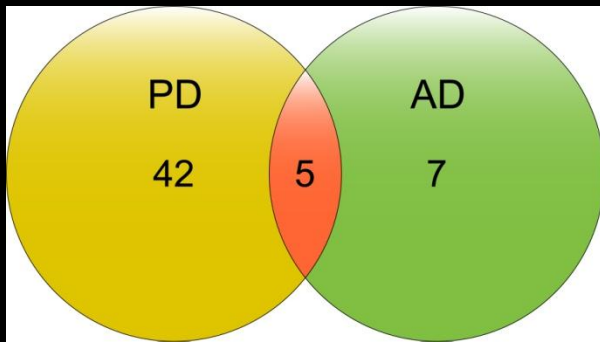
- ▶ **Peptoids are oligomers of N-substituted glycine units.** For the present work, we generated 8-mer peptoids constructed from 7 amines using the standard split-and-pool technique. Nser – *ethanolamine*, Npip – *piperonylamine*, Nasp – *glycine*, Nmba – (R)-*methylbenzylamine*, Nleu – *isobutylamine*, Nall – *allylamine*, Nlys – *diaminobutane*.

# Preliminary Data

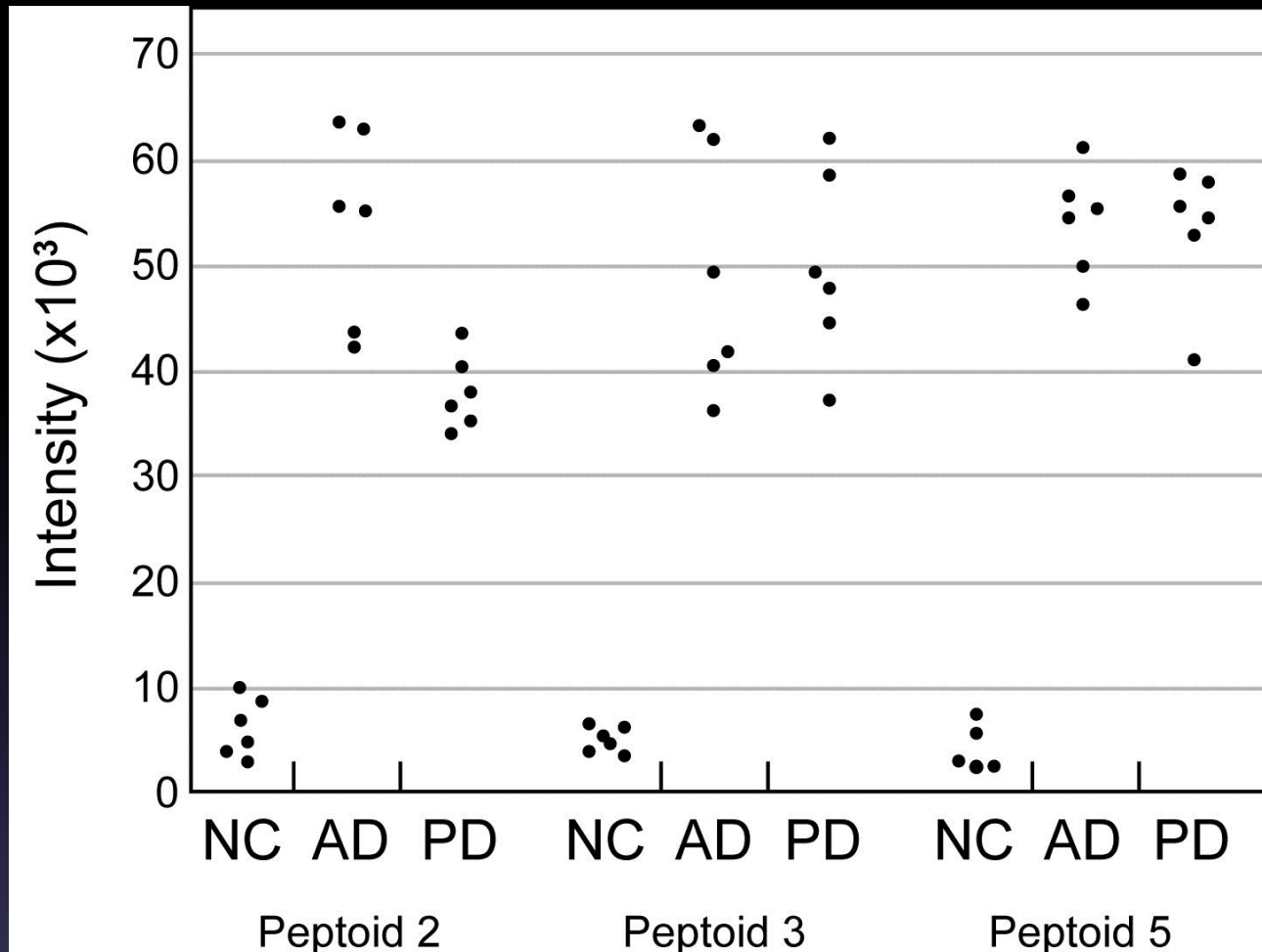
Group	Number	Age	Gender	CDR Stage/ Disease Duration
PD	6	$63 \pm 8$	3 M – 3 F	3-15 yr.
AD	6	$71 \pm 5$	3 M – 3 F	1-3
Control	6	$72 \pm 5$	3 M – 3 F	0



**Peptoids are printed onto glass slides, forming a microarray. We screened a library of 15,000 different peptoids from the total of 6 million. Blowups of portions of two microarrays to illustrate that many peptoid antibody markers are more intense in serum from an AD patient vs. a normal control. Illustrated (in blue boxes) is peptoid spot A2 on the array that is much more intense in the AD patient (60,993 intensity units) compared to the normal subject (4,386 intensity units). Serum samples, 15  $\mu$ g/ml, were hybridized overnight to the peptoid array, and spots are identified with a red fluorescent anti-human IgG.**

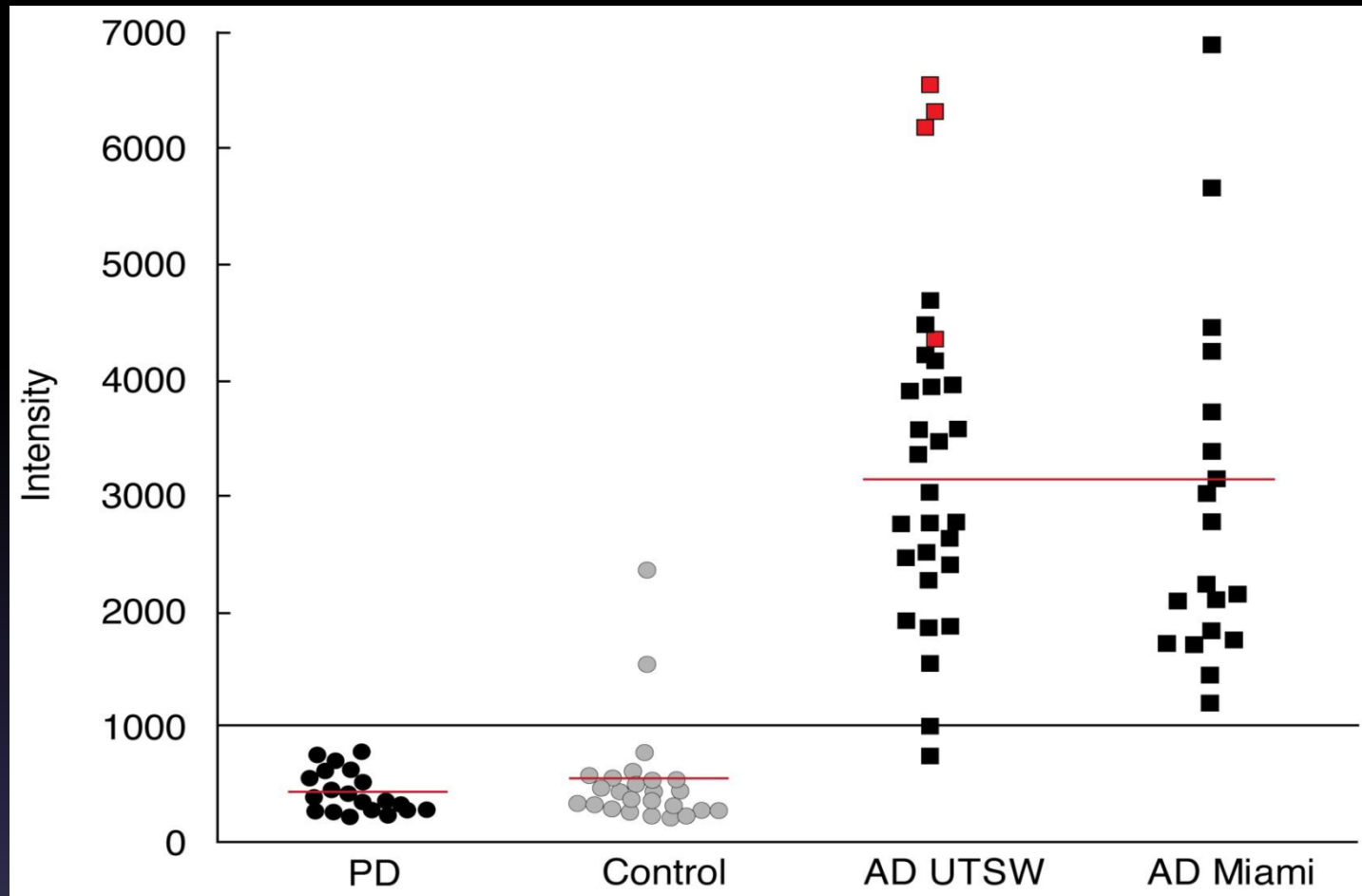


◆ **Three peptoids discriminate PD from AD and normal control (NC) subjects.** (Top Left) 42 peptoids were identified that are  $>2$ -fold higher in each PD vs. each AD and NC subject; 7 different peptoids were  $>2$ -fold higher in AD vs. the other two groups; and 5 different peptoids were  $>2$ -fold higher in both PD and AD vs. NC. (Right). 3 peptoids were identified that had the greatest magnitude of difference for the PD samples vs. the other two groups. These PD-peptoids are illustrated in the Lower Left panel.



Some peptoids are higher in both PD and AD serum vs. normal control (NC) samples. These peptoids may recognize antibodies that are common to neurodegenerative diseases, such as antibodies involved in neuroinflammation and neurodegeneration.





We have identified peptoids that recognize IgGs elevated in AD. Using 49 AD, 20 PD and 25 normal controls, the AD3 peptoid was shown to have high sensitivity and specificity for the identification of AD. Red dots are autopsy-confirmed AD cases.

# Summary

- PD-related antibodies (e.g., alpha-synuclein) have been identified in the blood from both normal and PD patients.
- Using peptoid technology, we can identify antibodies that are higher in the serum from PD patients vs. normal controls and those with AD.
- Our planned studies for the PDBP will (1) seek to identify PD-peptoids that discriminate serum from control and AD patients, (2) determine whether the peptoids can be used to track disease progression, and (3) identify the antibodies that are recognized by the PD-specific peptoids.

# Collaborators & Research Support

- **UT Southwestern**

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